

REMARKS

Reconsideration of the present application is respectfully requested in view of the following remarks. Claims 1-11 are pending and currently under examination in the application. No amendments are made by the present response.

Rejections Under 35 U.S.C. § 103

A. The Examiner rejects claims 1-5 under 35 U.S.C. § 103(a) for alleged obviousness over Herman *et al.* (U.S. Patent No. 5,786,146) in view of Gagna (U.S. Application No. 2003/0096273). The Examiner asserts that Herman *et al.* teach a bisulfite modification method for converting cytosine to uracil in a nucleic acid molecule, but agrees that Herman *et al.* fail to teach such a method wherein the nucleic acid molecule is bound to a solid phase. The Examiner asserts, however, that Gagna remedies this defect by teaching a method for immobilizing nucleic acid molecules on a solid phase, which supposedly allows the nucleic acid molecules to be used in *various assays*. Even though conceding that the cited references, alone or in combination, fail to teach incubating the solid phase bound deaminated nucleic acid molecule under alkaline conditions, as recited in step (d) of claim 1, the Examiner asserts that a person of ordinary skill in the art would have been motivated to apply the method of Gagna to the method of Herman *et al.*, and further asserts that such a combination would have been *prima facie* obvious at the time of filing.

B. The Examiner rejects claims 6-11 under 35 U.S.C. § 103(a) for alleged obviousness over Herman *et al.* in view of Gagna, in further view of Weindel *et al.* (WO 01/37291). The Examiner relies on Herman *et al.* and Gagna as described above, but agrees that these references do not disclose the use of a solid phase that comprises a magnetic glass particle, wherein the magnetic glass particle has a diameter between 0.5 and 5µm, or wherein the magnetic glass particle is manufactured by the sol-gel method. The Examiner asserts, however, that Weindel *et al.* disclose a magnetic glass particle for use in nucleic acid amplification and hybridization assays, and further asserts that a person of ordinary skill in the art would have been

motivated to use the glass particle of Weindel *et al.* according to the method of Herman *et al.* as a solid support because of the advantages described for using such particles.

Applicants traverse these rejections and submit that the instant claims satisfy the requirements of non-obviousness over the cited references. In particular, Applicants submit that the Examiner has not established a *prima facie* case of obviousness with respect to the presently claimed subject matter. (See *In re Mayne*, 104 F.3d 1339 (Fed. Cir. 1997); the USPTO has the burden of showing a *prima facie* case of obviousness). The Examiner must at a minimum demonstrate that the combined references teach or suggest all the claim features, and even assuming, *arguendo*, that the combination of references teaches each claim feature, the Examiner must provide an explicit, apparent reason to combine these features in the fashion claimed by the Applicant with a reasonable expectation of success. See *KSR v. Teleflex, Inc.*, No 04-1350 at 4, 14 (U.S. Apr. 30, 2007) (“A patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art”). Applicants also note that “[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” *Id.* at 14, citing *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006).

Here, the Examiner has failed to demonstrate that the cited references teach or suggest each feature of the instant claims and, in fact, recognizes that Herman *et al.* and Gagna both fail to teach or suggest the recited step of incubating a solid phase bound deaminated nucleic acid under alkaline conditions (see the Action, page 3). The Examiner also fails entirely to provide any articulated reasoning that a person of ordinary skill in the art would combine the cited references with a reasonable expectation of success, but relies instead on mere conclusory assertions that the instant claims are *prima facie* obvious over the cited references.

Herman *et al.* fail to teach or suggest each feature of the instant claims. In particular, as conceded by the Examiner, Herman *et al.* fail entirely to teach or suggest the use of a solid phase support in bisulfite modification reactions, and fail as well to teach or suggest the step of incubating a solid phase bound deaminated nucleic acid under alkaline conditions.

Gagna does not remedy the defects in Herman *et al.* Gagna is entirely silent on the use of the solid phase techniques described therein for use in bisulfite modification reactions. Gagna, at best, mentions that solid phase immobilization may be used in *various assays*, but this generic teaching is far more limited than appreciated by the Examiner. For example, Gagna, in particular, suggests that the utility of the invention described therein relates merely to allowing the characterization of the physical, chemical, and structural properties of non-denatured nucleic acid molecules (*see, e.g.*, page 1, paragraph 0008 of Gagna), which utility in no way relates to chemically modifying nucleic acid molecules, as recited in the instant claims. Applicants also note that none of the exemplary uses described in Gagna relate to modifying nucleic acid molecules, as presently claimed. Gagna, therefore, fails to teach or suggest the use of solid phase immobilization, as described therein, with a nucleic acid modification reaction, such as with the bisulfite reaction recited in the instant claims.

With regard to claims 6-11, Weindel *et al.* fail to remedy the defects in both Herman *et al.* and Gagna, as Weindel *et al.* are limited to teaching the use of the magnetic glass particles described therein for either nucleic acid purification protocols or standardized nucleic acid amplification reactions. Weindel *et al.* are, thus, silent on performing bisulfite modification reactions on a solid phase support, let alone on a magnetic glass particle, as recited in claims 6-11. As such, none of the cited references, alone or in combination, teach or suggest each feature of the instant claims and, thus, fail to establish the minimum requirements of a *prima facie* case of obviousness with respect to the presently claimed subject matter.

In addition, both Gagna and Weindel *et al.* fail to motivate a person of ordinary skill in the art to conduct the bisulfite reaction of Herman *et al.* on solid phase-bound nucleic acid molecules with any reasonable expectation of success. Indeed, the Examiner has failed entirely to provide any articulated reasoning to support the instant obviousness rejection, especially, as required, in regard to finding a reasonable expectation of success. Notwithstanding the absence of this required reasoning, Gagna and Weindel *et al.* clearly fail to provide any such motivation. For one reason, nucleic acid characterization and purification assays, as described in Gagna and Weindel *et al.*, are technically distinct from bisulfite modification reactions, as recited in the instant claims. In fact, the method of Gagna requires that the solid-phase bound nucleic

acid is undenatured, in contrast to Hermann *et al.*, which requires denatured nucleic acids, making the teachings of these two references technically incompatible in the mind of a person skilled in the art at the time of invention. In addition, Gagna teaches that nondenatured nucleic acid molecules should be first synthesized externally, using known techniques, and then immobilized onto the solid support surface (*see, e.g.*, page 1, paragraph 0008 of Gagna), suggesting that the solid phase immobilization methods described therein are not necessarily suitable for the type of chemical reactions as presently claimed. Further according to the method of Gagna, nucleic acid binding to the solid support is irreversible (*see, e.g.*, paragraphs 0023-0025 of Gagna), which property contrasts to the solution offered by the present invention. Applicants submit herewith the Declaration of Dr. Christine Market-Hern, which further enunciated these non-obvious differences of the present invention over the teachings of the cited prior art references.

Similarly, Weindel *et al.* fail to motivate a person skilled in the art to combine the methods provided therein with Hermann *et al.* For example, Weindel *et al.* teach that certain nucleic acid modification reactions, such as with 5'-nuclease technology, “occur in solution phase, *i.e.* without solid phase immobilisation” (*see, e.g.*, Experiment 7.1.2 of Weindel *et al.*), suggesting that the solid phase immobilisation technique described therein is not necessarily suitable for certain reactions, such as the bisulfite reaction recited in the instant claims.

The same conclusion is supported by the fact that according to Weindel *et al.* the binding of nucleic acids to magnetic glass particles is performed solely with the intention to purify the nucleic acid from contaminating substances (*see, e.g.*, Weindel *et al.*, at page 1, lines 1 to 6, and page 13, third paragraph), as opposed to subjecting the nucleic acid to any chemical reaction, as in the case of Hermann *et al.* or the present invention.

Moreover, according to the general understanding in the art at the time of filing, a person of ordinary skill in the art would have understood that bisulfite reactions could not be successfully carried out using solid phase-bound nucleic acid molecules. In explanation, when performing a conventional bisulfite reaction as understood at the time of filing, the nucleic acid molecules were denatured, since bisulfite can only react with pyrimidines that are not involved in base pairing (*see, e.g.*, page 3, lines 30-32 of the specification). In other words, it was

understood at the time of filing that the pyrimidines in double-stranded molecules were not susceptible to bisulfite modification. But when nucleic acid molecules are bound to a solid phase, such as glass, they interact with the solid phase, and conventional knowledge at the time of filing suggested that these interactions caused the nucleic acid molecules to behave like double-stranded nucleic acids (*see* Declaration of Dr. Christine Markert-Hahn). In particular, Dr. Markert-Hahn stated:

"Since bisulfite reacts only with unmethylated cytosines that do not participate in base pairing (i.e., single stranded DNA), a person skilled in the art would have been surprised to learn that a bisulfite reaction could be accomplished using a single stranded DNA bound to a solid phase. In fact, at the time the invention, my co-worker and I were also very surprised when we found out that the single stranded DNA bound to a solid phase could actually be accessed successfully by the bisulfite ions. The teachings of the above cited references would not have changed my surprise in this matter."(see Declaration of Dr. Christine Markert-Hahn, page 9, last paragraph bridging page 9, first paragraph).

Accordingly, a person of ordinary skill in the art at the time of filing would not reasonably expect nucleic acid molecules bound to a solid phase to be susceptible to bisulfite modification, since the pyrimidines, behaving as in a double-stranded nucleic acid molecule, would not be expected to react with bisulfite. This understanding would necessarily prevent a person of ordinary skill in the art from attaching nucleic acid molecules destined for bisulfite reactions to a solid support, as recited in the instant claims.

Hermann *et al.* and Gagna, even in view of Weindel *et al.*, thus, not only fail to motivate a person of ordinary skill in the art to combine their limited teachings in arriving at the presently claimed subject matter, but fail as well to provide a reasonable expectation of success in performing the same. Applicants submit that the bisulfite reactions utilizing nucleic acid bound to a solid phase, as presently claimed, represent an entirely unexpected and surprising result at the time of filing the instant application, as evidenced by the accompanying Declaration of Dr. Christine Markert-Hahn. Applicants also submit that the only way the Examiner can assert that the instant claims are obvious over the cited references is by relying on the disclosure in the instant application and, therefore, by relying on impermissible hindsight.

Based on the remarks provided herein, Applicants submit that claims 1-11 satisfy the requirements of non-obviousness under 35 U.S.C. § 103(a), and respectfully request reconsideration and withdrawal of this rejection to the claims.

Applicants believe that all of the claims in the application are allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Respectfully submitted,
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Enclosures:
Declaration of Dr. Christine Market-Hahn

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